REMARKS

Applicants have amended claims 38, 68, and 94 to recite an algorithm that can be used to determine percent identity, as requested by the Examiner. Attached hereto is a marked-up version of the changes made to the specification by the current amendment, captioned "Version With Markings to Show Changes Made." Support for these amendments can be found throughout the specification as filed, for example, on page 12, lines 3-7. No new matter has been added.

Upon entry of the following amendments, claims 21-56 and 58-103 will be pending.

I. Rejections under 35 U.S.C. §101

Claims 21-56 and 58-103 remain rejected under 35 U.S.C. § 101, as allegedly lacking a "credible, substantial, specific, or well established utility." *See* page 2, section 2 of Paper No. 30. Specifically, it is asserted that:

> ...Applicant has not shown that the recited proteins actually bind FK506, but only speculate the presence of this property in the polypeptides set forth as SEQ ID NO:s 6 and 8 based on sequence homology. However, even if said polypeptides bind FK506, and are in fact a member of the FKBP family, the function or utility will not have been established. The Collins et al article attached to the Applicant's amendment filed on 4-29-02, comments on the functional diversity of FKBP family members, and that though at the time of its publication FKBP65 was identified as a member of the FKBP based on sequence homology (the presence of three PPIase domains), the possible functions of FKBP65 were still unknown (see entire article, especially the last two paragraphs of the article).

Applicants respectfully disagree and traverse this rejection.

The issue in the present case is whether the instant application explicitly teaches at least one utility that meets the requirements of § 101. Applicants submit that the specification as filed provides a specific, substantial, credible and well established utility for the polypeptides set forth as SEQ ID NO:s 6 and 8 in the instant specification, namely, to bind the macrolide antibiotic FK506. Regarding the Examiners statement that "Applicant has not shown that the recited proteins actually bind FK506," Applicants submit that proof of a specific or substantial utility is not the proper legal standard upon which to evaluate utility. The proper standard is a reasonable correlation, not a statistical certainty, such that one of skill in the art would find the proposed utility more likely than not true (*see* M.P.E.P. 2107.03, page 2100-43, section I). The proper legal standard to judge utility does not rest upon whether data is disclosed, rather, the standard is whether one of skill in the art, upon

reading the entire specification, would find the asserted utilities for the claimed invention an "inherently unbelievable undertaking or involve implausible scientific principle" (*see In re Brana*, 51 F.3d 1560, 1566 (Fed Cir. 1995)). Applicants respectfully submit that the present asserted utility of binding FK506 is not implausible to one of skill in the art based on the following facts:

1. The proteins of the instant invention exhibit significant sequence homology with FKBP65, which binds FK506 (*see* specification page 6, lines 19-39 and page 7, lines 2 through 27).
2. The proteins of the instant invention possess conserved PPIase domains present in all other FKBP's (*see* page 6 of Applicants previous response dated April 29, 2002).
3. The proteins of the instant invention possess the seven conserved amino acid residues shared among all FKBP's that have been identified, these amino acid residues being thought to be involved in FK506 binding interactions (*see* Applicants prior response, page 6, and Coss *et al.* at page 29337).

Rather, the asserted utility that the proteins of the instant invention are FKBPs that bind FK506 is clearly and reasonably correlated such that one of skill in the art would find it more likely than not true. In fact, as acknowledged by the Examiner on page 3 of Paper No.30, at the time of its publication in a peer-reviewed journal, the FKBP65 protein disclosed in the Coss *et al.* manuscript submitted in Applicant's response dated April 29, 2002 was believed to be a member of the FKBP family based on sequence homology and the presence of the PPIase domains (see page 29337, Results section in Coss *et al.*).

Regarding the Examiner's contention that even if the claimed polypeptides bind FK506, and are in fact a member of the FKBP family, the functions or utility will not have been established, Applicants respectfully disagree. It is well established that the FKBP's are a distinct class of highly conserved intracellular receptors termed immunophilins, which exhibit peptidylprolyl *cis-trans*-isomerase (PPIase) activity that is inhibited upon binding to the immunosuppresant macrolide antibiotics FK506 or rapamycin (*see* Coss *et al.*, submitted as Exhibit C with Applicants' response dated April 29, 2002, and references therein). Binding to FK506 or rapamycin and exhibiting PPIase activity are shared, characteristic, well-established functions of the FKBP's. Furthermore, it is also well known that FK506 and rapamycin exert their immunosuppressive effects by blocking signal transduction pathways in normal T cells, thus inhibiting T-lymphocyte growth and differentiation (*see* Coss *et al.* (1995) page 29336, column 2). Contrary to the Examiners allegation, this publication does not dispute the well established functions of FKBP's- namely binding to FK506 or rapamycin

and possessing PPIase activity that is inhibited by such binding. The functional diversity discussed in the last two paragraphs of the Coss *et al.* manuscript is in relation to the differences in FKBP's subcellular localization and association with various additional intracellular protein complexes. These last two paragraphs of Coss *et al.* further discuss the potential to identify further proteins that bind FKBP65 as well as other genes related to FKBP65. This information is merely elucidating the downstream molecular pathways that FKBP's may employ once bound to FK506 in order to effect inhibition of T lymphocyte growth and differentiation. Applicants respectfully submit that such information is merely mechanistic, which is not a requirement for satisfying utility under § 101 *(see* e.g., *Newman v. Quigg*, 11 U.S.P.Q.2d 1340, 1345 (Fed. Cir. 1989)). Any differences that various immunophilins may exhibit in their subcellular localization or interaction with additional proteins do not change the fact that FKBP binding to FK506 leads to immunosuppression by inhibiting T cell proliferation and/or differentiation or that FKBP PPIase activity is inhibited by such binding.

Applicants respectfully disagree with the Examiner's assertion that "function of a polypeptide cannot be established solely on the basis of the presence of PPIase domains" (*see* page 3, lines 6-8 of Paper No.30). Applicants respectfully submit that such PPIase domains are consensus sequences found in all FKBP's (*see* page 29337 of Coss *et al*). Furthermore, Coss *et al.* teaches that it was known in the art that within these PPIase domains are found the 7 conserved amino acid residues important for imparting FKBP function, namely binding FK506 (*see* Coss *et al.*, p.29337).

Applicants submit that the asserted function of the proteins of the instant invention is not based solely on the presence of PPIase domains, but also on overall sequence homology to FKBP65 and the presence of the conserved amino acid residues involved in FK506 binding, as pointed out above. Together, such characteristics as nucleotide sequence percent identity and the presence of conserved PPIase domains and residues have been used by those of skill in the art when classifying other members of the FKBP family (see Jin *et al.* PNAS, 88:6677-6681 (1991) submitted herewith as Exhibit A; and Coss et al. (1995) submitted as Exhibit C with Applicants' response dated April 29, 2002). As mentioned above, sequence homology and the presence of conserved PPIase domains were acceptable criteria by which to classify FKBP65 as an FKBP in a peer-reviewed journal (*see* Coss et al. (1995)). Thus, Applicants submit that the overall sequence homology between the proteins of the instant invention and FKBP65, in addition to the presence of conserved PPIase domains and amino acid residues important for FK506 binding would lead one skilled in the art to find it more

likely than not that the proteins of the instant invention are, in fact, novel members of the FKBP family and that they do bind FK506 as stated on page 1, lines 13-14 and 34 of the specification. Moreover, since FK506 binding proteins are a class of well-established and useful proteins, assignment of a new protein to a class of well-known and sufficiently conserved proteins imputes the same well-established utility to the claimed protein of the invention as is clearly taught in the specification (*see* page 5, lines 10-16 and lines 19-25) and would be understood by one of skill in the art.

Based on the above facts, Applicants submit that the instant specification as filed does explicitly teach at least one credible, substantial, specific, or well-established utility, which is to bind FK506. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 101, for alleged lack of utility, be reconsidered and withdrawn.

II. Rejections under 35 U.S.C. §112, first paragraph- Enablement

Claims 21-56 and 58-103 are also rejected under 35 U.S.C. §112, first paragraph allegedly for lack of enablement. (*See* page 2, section 2 of Paper No. 30). More particularly, the Examiner states that since the claimed invention is allegedly not supported by either a specific or well established utility, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Applicants respectfully disagree and traverse.

For the reasons discussed above in response to the rejection under 35 U.S.C. § 101, the claimed invention is supported by a well-established utility. The Examiner "should not impose a 35 U.S.C. § 112 , first paragraph, rejection grounded on 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." M.P.E.P. § 2107(IV) at 2100-28 (Rev. 1, Feb. 2000). Since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection of the claims under 35 U.S.C. § 112, first paragraph, based on lack of utility of the claimed invention, should be withdrawn.

III. Rejections under 35 U.S.C. §112, first paragraph- Written description

Applicants believe that the Examiner has withdrawn the rejection to claims 38-51 and 68-80 under 35 U.S.C. 112, first paragraph- written description. However, in section (4) on page 3 of Paper No. 30, following the word "WITHDRAWN," it is written that "Claims 38-51 and 68-60 are also rejected under 35 U.S.C. 112..." Applicants have not responded to this rejection, as it appears to have been withdrawn, but Applicants are confused by the use of the

present tense to describe the status of this rejection. Applicants respectfully request confirmation from the Examiner that this rejection has been withdrawn.

Regardless, Applicants maintain that the claimed invention satisfies the requirements for written description under 35 U.S.C. §112, first paragraph for the reasons argued in pages 8 and 9 of Applicants previous response dated April 29, 2002.

IV. Rejections under 35 U.S.C. §112, second paragraph

Claims 38-51 and 68-80 are rejected as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states on page 3, section 7 of Paper No. 30:

> Claims 38-51, 68-80 and 94-103 are indefinite in their recitation of the phrase "at least 95% identical" recited in independent claims 38, 68 and 94. It is noted that the instant specification discloses the phrase "percent identity" on page 13 can be defined using one of several known computer programs. Incorporating one of these algorithms into the instant claims, would overcome this rejection.

Applicants submit that independent claims 38, 68 and 94 have been amended to recite "wherein % identity is determined using the BESTFIT computer program," thereby overcoming this rejection. Thus, Applicants respectfully request that this rejection be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully request that the remarks above be entered and made of record in the file history of the instant application. Applicants believe that all objections and rejections have been obviated or overcome and the claims are in condition for allowance.

If there are any fees due in connection with the filing of this paper, please charge such fees to Deposit Account No. 08-3425.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ruben et al.

Application No.: 09/225,502 Group Art Unit: 1644

Filed: January 6, 1999 Examiner: A. Decloux

For: Human FK506 Binding Proteins

VERSION WITH MARKINGS TO SHOW CHANGES MADE

38. (Once amended) An isolated nucleic acid molecule encoding a first amino acid sequence at least 95% identical to the entire length of a second amino acid sequence selected from the group consisting of:

(a) an amino acid sequence encoding amino acid residues 1 to 574 or SEQ ID NO:6;

(b) a nucleotide sequence encoding amino acid residues 2 to 574 of SEQ ID NO:6;

(c) an amino acid sequence encoding amino acid residues 25 to 574 of SEQ ID NO:6; and

(d) an amino acid sequence encoding amino acid residues 1 to 388 of SEQ ID NO:8;

wherein % identity is determined using the BESTFIT computer program, and wherein said nucleic acid molecule encodes a polypeptide that binds FK506.

68. (Twice amended) An isolated nucleic acid molecule encoding a first amino acid sequence at least 95% identical to the entire length of a second amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of the full-length polypeptide encoded by the cDNA contained in clone HSYBM46 as deposited with the ATCC as accession number 209193,

(b) the amino acid sequence of the full-length polypeptide, lacking the N-terminal methionine, which is encoded by the cDNA contained in clone HSYBM46 as deposited with the ATCC as accession number 209193,

(c) the amino acid sequence of the secreted portion of the polypeptide encoded by the cDNA contained in clone HSYBM46 deposited with the ATCC as accession number 209193;

wherein % identity is determined using the BESTFIT computer program, and wherein said nucleic acid molecule encodes a polypeptide that binds FK506.

94. (Twice amended) An isolated nucleic acid molecule encoding a first amino acid sequence at least 95% identical to the entire length of an amino acid sequence of the polypeptide encoded by the cDNA contained in clone HFKBC47 as deposited with the ATCC as accession number 209193; wherein % identity is determined using the BESTFIT computer program, and wherein said nucleic acid molecule encodes a polypeptide that binds FK506.